

What is claimed is:

1. A method of producing an activated ester of polyethylene glycol (PEG), comprising the step of activating PEG with N,N'-disuccinimidyl oxalate or 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate under the appropriate conditions.
2. The method according to claim 1, comprising the step of activating PEG with N,N'-disuccinimidyl oxalate.
3. The method according to claim 2, wherein the ratio of N,N'-disuccinimidyl oxalate to PEG is 30 :1 or less.
4. The method of producing a N,N'-disuccinimidyl ester of polyethylene glycol (PEG) according to claim 2, wherein an organic base is used as a catalyst.
5. The method of producing a N,N'-disuccinimidyl ester of polyethylene glycol (PEG) according to claim 4, wherein the base catalyst is selected from the group consisting of pyridine and N,N'-4-dimethylaminopyridine.
6. A method of producing a PEG-nucleophile conjugate, comprising of reacting the PEG active ester of claim 2 with a biologically active nucleophile under appropriate conditions to form a PEG-nucleophile conjugate.
7. A method of producing a PEG-linker-nucleophile conjugate, comprising the steps :
  - (a) reacting the PEG active ester of claim 2 with a linker;
  - and
  - (b) reacting the resulting PEG-linker with a biologically active nucleophile under appropriate conditions to form a PEG-linker-nucleophile conjugate.
8. The method according to claim 6 or 7 wherein said biologically active nucleophile is a peptide or a protein.
9. The method according to claim 8, wherein said PEG active ester is reacted with said peptide or protein in the molar ratio of between 1 and 30 moles active ester to 1 mol protein or with said

linker in the molar ratio of 1 mole active ester to 1 to 10 moles linker.

10. The method according to claim 7, wherein the PEG-linker(s) conjugate is activated with N,N'-disuccinimidyl oxalate, and subsequently reacted with a peptide or protein in the molar ratio of between 1 and 30 moles active ester to 1 mol peptide or protein to form PEG-linker(s) peptide or protein conjugate
11. The method according to claim 1, comprising the step of activating PEG with 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate.
12. The method according to claim 11, wherein the ratio of 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate to PEG is 30 :1 or less.
13. The method of producing a 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] ester of polyethylene glycol (PEG) according to claim 11, wherein an organic base is used as a catalyst.
14. The method of producing a 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] ester of polyethylene glycol (PEG) according to claim 13, wherein said base catalyst is selected from the group consisting of pyridine and N,N'-4-dimethylaminopyridine.
15. A method of producing a PEG-nucleophile conjugate, comprising of reacting the PEG active ester of claim 11 with a biologically active nucleophile under appropriate conditions to form a PEG-nucleophile conjugate.
16. A method of producing a PEG-linker-nucleophile conjugate, comprising the steps :
  - (a) reacting the PEG active ester of claim 11 with a linker; and
  - (b) reacting the resulting PEG-linker with a biologically active nucleophile under appropriate conditions.
17. The method according to claim 15 or 16 wherein said biologically active nucleophile is a peptide or a protein.
18. The method according to claim 17, wherein said PEG active ester is reacted with said peptide or protein in the molar ratio of

between 1 and 30 moles active ester to 1 mol protein or with said linker in the molar ratio of 1 mole active ester to 1 to 10 moles linker.

19. The method according to claim 16, wherein the PEG-linker(s) conjugate is activated with 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate, and subsequently reacted with a peptide or protein in the molar ratio of between 1 and 30 moles active ester to 1 mol peptide or protein to form PEG-linker(s) peptide or protein conjugate.
20. A PEG-nucleophile or PEG-linker-nucleophile conjugate prepared according to claim 6 or 7, wherein said nucleophile is an hGH antagonist or an anti TNF $_{\alpha}$  antibody.
21. A PEG-nucleophile or PEG-linker-nucleophile conjugate prepared according to claim 15 or 16, wherein said nucleophile is an anti TNF $_{\alpha}$  antibody or an hGH antagonist.
22. The conjugate of claim 21 wherein said TNF $_{\alpha}$  antibody is a CDR-grafted, hTNF40-based modified Fab.
23. A composition comprising of a PEG-nucleophile conjugate, with or without a linker, prepared according to claim 6, 7, 15, or 16.
24. A composition comprising of a PEG-nucleophile conjugate, with or without a linker, prepared according to claim 20.
25. A composition comprising of a PEG-nucleophile conjugate, with or without a linker, prepared according to claim 21.
26. A composition comprising of a PEG-nucleophile conjugate, with or without a linker, prepared according to claim 22.
27. A method of treating a patient in need thereof with a PEG-nucleophile conjugate, with or without a linker, according to claim 20.
28. A method of treating a patient in need thereof with a PEG-nucleophile conjugate, with or without a linker, according to claim 21.

29. A method of treating a patient in need thereof with a PEG-nucleophile conjugate, with or without a linker, according to claim 22.